PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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31 March 95

PATENTS ORDERED

PCT

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NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	
27 MAR 1995	
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
P/2234-2	

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US93/12639	29 DECEMBER 1993	31 DECEMBER 1992

Applicant

RAMOT UNIVERSITY AUTHORITY FOR APPLIED RESEARCH AND INDUSTRIAL DEVELOPMENT LTD.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ROBERT D. BUDENS
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Form PCT/IPEA/416 (July 1992)*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US93/12639

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

☐ the international application as originally filed.

☒ the description, pages 1-20 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.
pages _____ , filed with the letter of _____.

☒ the claims, Nos. 1-7 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. 8-29 , filed with the demand.
Nos. NONE , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

☒ the drawings, sheets/~~fig~~ 1-7 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE.

☒ the claims, Nos. NONE.

☒ the drawings, sheets/~~fig~~ NONE.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rul 70.2(c)).

4. Additional observations, if necessary:

NONE

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Th question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 18, 25-29

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _ are so unclear that no meaningful opinion could be formed *(specify)*.

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 18, 25-29 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	5-6, 16-17, 20-21, 24	YES
	Claims	1-4, 7-15, 19, 22-23	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-17, 19-24	NO
Industrial Applicability (IA)	Claims	1-17, 19-22	YES
	Claims	23-24	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-4, 7-15, 19 and 22-23 lack novelty under PCT Article 33(2) as being anticipated by Celada et al. Celada et al. discloses epitopes and antibodies which bind to viral epitopes. In particular, Celada et al. discloses the monoclonal antibody designated mAb 55. The binding of mAb 55 to CD4 is enhanced when the CD4 molecule is bound to gp120 (see page 1143, first column, first paragraph and page 1146, paragraph bridging columns 1-2). Thus, Celada et al. discloses to the public that which is set forth and claimed in the instant application.

Claims 1-2 and 10-12, 15, 19 and 22 lack novelty under PCT Article 33(2) as being anticipated by any of Ortega-Pierres et al. or Javid et al. or Nordfang et al. or Lind et al.(Abstract 207470) or Lind et al. (Abstract 407661) or Boreham et al. Each of the cited references and Abstracts discloses antigen-antibody systems which result in the exposure of "hidden" epitopes subsequent to binding of the so-called "binding couple." Further, the references teach antibodies which immunologically bind to said "hidden epitopes." Further, as these epitopes are "hidden" in the absence of formation of the "binding couple", one of ordinary skill in the art would reasonably conclude that antibodies to the "hidden" epitopes would necessarily bind to the binding couple at least 10 times greater than to either of the members of the binding couple individually. Thus, each of the references appears to disclose to the public that which is set forth and claimed in the instant application.

Claims 1-17 and 19-24 lack an inventive step under PCT Article 33(3) as being obvious over Celada et al. The teachings of Celada et al. have been discussed above. Celada et al. does not specifically teach the monoclonal antibody designated CG-10 of the instant application. However, Celada et al. does teach epitopes and monoclonal antibodies as discussed above and suggests that "for example, after binding to gp120, changes in conformation could reshuffle the fine antigenic structure, and new or modified epitopes associated with distinct functional states of the molecule may come into existence (see page 1143, first paragraph). Thus, absent convincing objective evidence to (Continued on Supplemental Sheet.)*

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-17 and 19-24 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s): Claims 1-12 are vague and indefinite in the recitation "binding couple" since it is unclear what compositions are intended to be encompassed in the terminology "binding couple". Further, Claims 1-17 and 19-24 are vague and indefinite in the recitation "more accessible to antibodies or resumes a new conformation" since it is unclear how the epitope can "resume" a "new" conformation. Further, Claims 1-17 and 19-24 are vague and indefinite in the recitation "substantially" since it is unclear what level of increased accessibility to antibodies would constitute a "substantially" increased accessibility to antibodies.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(6): A61K 39/395, 39/42; C07K 7/00, 16/10; C12N 5/20 and US Cl.: 424/130.1, 148.1, 160.1; 435/70.21, 172.2, 240.27; 530/300, 350, 387.1, 388.1, 388.35, 388.75, 389.4, 389.6.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
the contrary, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the teachings of Celada et al. to produce additional antibodies to viral epitopes created or exposed after binding to gp120 and to use the antibodies, either alone or conjugated to a cytotoxic substance (i.e., an immunotoxin) as pharmaceutical reagents for use in methods for treating patients with HIV infections. One would be motivated by the teachings of Celada et al. and the long felt need for improved immunotherapeutics for HIV infection and would have had a reasonable expectation of success in obtaining antibodies having the same or similar properties as the CG-10 antibody of the instant invention since the epitopes exposed by gp120-CD4 interactions would be a necessary property of those interacting proteins and would necessarily reveal the same epitopes as recognized by the CG-10 antibody of the instant application.

Claims 23-24 lack industrial applicability as defined by PCT Article 33(4). Claims 23-24 are directed to a pharmaceutical composition and a method of treating patients with a viral infection, especially HIV, by administering antibodies of the claimed invention. However, there is no evidence in the description to establish that the pharmaceutical composition and method could indeed be used as claimed. It is well known in the art that retroviral infections in general, and HIV in particular, are refractory to therapy. Indeed, it is well known in the art that patients having an HIV infection produce neutralizing antibodies to gp120 which bind to various epitopes associated with viral binding, i.e., CD4-binding regions, yet these antibodies fail to prevent the progression of the infection. Therefore, absent evidence to the contrary, Applicant's claimed invention is deemed to be inoperable and thus lacking industrial applicability.

Note that newly added claims 18 and 25-29 are directed to inventions which were not searched in the Chapter I Search Report, and therefore have not been further treated on the merits, as no international preliminary examination report will be established on inventions which have not been previously searched.

---------- NEW CITATIONS ----------
NONE

8. An epitope according to claim 2, being revealed after binding of gp120 to an anti-gp120 antibody.

9. An epitope according to claim 8, consisting of a sequence present in the gp120 protein.

10. An antibody having binding specificity to an epitope according to claim 1.

11. An antibody according to claim 10, having a binding affinity to a complex formed between two members of a binding couple, which is at least 5 fold higher than its binding affinity to either of the two members by themselves.

12. An antibody according to claim 10, having a binding affinity to a complex formed between two members of a binding couple, which is at least 10 fold higher than its binding affinity to either of the two members by themselves.

13. An antibody according to claim 10, directed against an epitope which is revealed after binding of the HIV gp120 protein to the CD4 protein.

14. An antibody according to claim 13, directed against an epitope which consists of a sequence of the gp120 protein.

15. An antibody according to claim 10, being a monoclonal antibody.

16. An antibody according to claim 15, being the CG-10 antibody.

17. An antibody having a binding affinity similar to that of the antibody of claim 16.

18. An anti-idiotype antibody of a mAB according to claim 10.

19. A hybridoma capable of secreting a monoclonal antibody according to claim 15.

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20. A hybridoma according to claim 19, deposited with the European Collection of Animal Cell Culture (ECACC) under the accession number 93020415.

21. An antibody according to claim 10, being conjugated to a cell cytotoxic substance.

22. An antibody according to claim 10, being conjugated to a detectable marker.

23. A pharmaceutical composition for treating a viral infection comprising an antibody according to claim 10.

24. A method for treating a viral infection, comprising administering to a patient an effective amount of an antibody according to claim 10.

25. A method of diagnosis of a viral infection, comprising contacting the cells susceptible of viral infection with an antibody of claim 10, and then detecting the presence of the antibodies on the cells' surface.

26. A method according to claim 25, wherein the cells are withdrawn from the patient and contacted with the antibodies *in vitro*.

27. A method of diagnosis of a viral infection, comprising contacting a body fluid sample with an antibody according to claim 10, and detecting the formation of immunocomplexes involving said antibody or said conjugate.

28. A method for the detection of the presence in a body fluid of antibodies specific for an epitope according to claim 1, comprising contacting the body fluid or an antibody containing fraction thereof, with an anti-idiotype antibody according to claim 18.

29. A method for immunizing an animal against a viral infection comprising administering to a subject an effective amount of an epitope according to claim 3, or an anti-idiotype antibody of said epitope.